

REMARKS/ARGUMENTS

Applicant notes the Examiner's withdrawal of the rejection of claims 22 and 25, as being unpatentable under 35 U.S.C. §102(b) and 35 U.S.C. §103(a), respectively, over Fawwaz et al., J. Nuclear Medicine, Proc. Of the 36th Annual Meeting, vol. 30 p 935-936 (1989). Applicant thanks the Examiner for withdrawing these rejections.

Rejections under 35 U.S.C. §103

The Examiner rejects claims 22 and 25 under 35 U.S.C. §103(a) as being unpatentable over WO 93/21957. Applicant respectfully disagrees with Examiner's assessment of the reference.

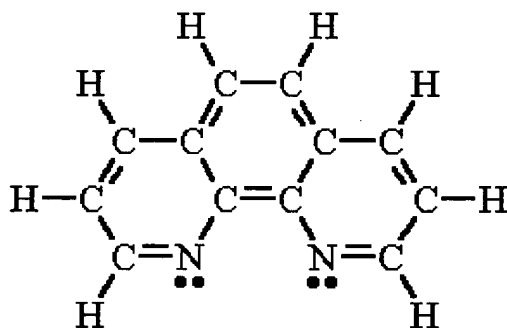
According to the Examiner, this reference discloses conjugates comprising a metal radionuclide ion (which can be Tc, Re and Mn), a complexing agent (which can be phenanthroline) and an immunoreactive group (which can be a variety of different antibodies, proteins, hormones, etc.).

With careful attention to the claims at issue, the Examiner will note that the claims of the present invention do not require a "complexing agent." Rather, the present claims require an intercalating agent. The terms are not synonymous. A chelator is a molecule that binds two or more ions, such as, for example, metal ions. An intercalating agent, on the other hand, is a chemical substance that has a structure such that it can insert itself in between adjacent nucleotides of a DNA molecule.

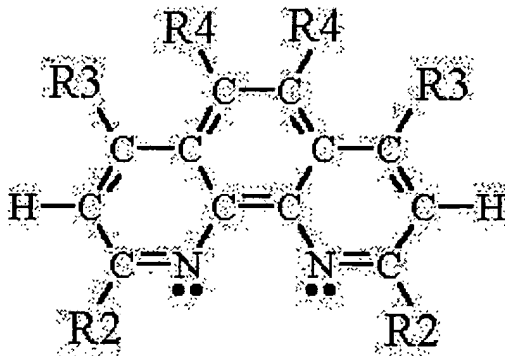
The Examiner states that the "complexing agent" of the cited reference may be

phenanthroline, and thus the Examiner may be of the view that the inclusion of phenanthroline satisfies the requirement for an intercalating agent in the present application, whether phenanthroline is identified as an intercalating agent or a complexing agent in the cited art. It is not, however, the case that the cited reference discloses phenanthroline. Rather, the reference discloses the use of phenanthroline derivatives as complexing agents (see, for example, page 6, first paragraph under "Summary of the Invention," which indicates that the invention comprises "derivatives" of phenanthroline; see also page 11, third paragraph under "Description of Preferred Embodiment," which indicates that the invention comprises "derivatives" of phenanthroline; see also the "Abstract," which refers to providing "novel phenanthrolines," which necessarily indicates phenanthroline derivatives because phenanthroline itself was already known).

Phenanthroline generally has the following structure:



The phenanthroline derivative disclosed in the cited reference has the following structure (see page 8, A-IV):



wherein:

R2 = hydroxy, carboxy, hydroxyalkyl, thioalkyl, carbonyliminoacetic acid, methyleneiminoacetic acid, methylenethioethyleneiminoacetic acid, carboxyalkythioalkyl, hydrazinylidenediacetic acid, or a salt of such acids, or two R2 groups, taken together, represent the atoms necessary to complete a macrocyclic ring structure containing at least one heteroatom coordinating site and at least one, preferably two, alkylene groups forming part of the ring structure;

R3 = hydrogen, alkyl, alkoxy, alkylthio, alkylamino, alkylformamido, aryloxy, heterocycl, or a protein reactive group; and

R4 = hydrogen or a protein reactive group.

The distinction is significant. With respect to R2, particularly, it is clear that phenanthroline itself is not disclosed in cited reference, for in no instance may R2 be merely a hydrogen atom. Further, Applicant submits that it would not be obvious from the cited reference to use phenanthroline in the present invention. This goes again to the difference between

complexing agents and intercalating agents. The Examiner has provided no evidence that the phenanthroline derivatives disclosed in the reference, with their unwieldy substituents attached to the basic ring structure, would be able to perform as intercalating agents. The Examiner's conclusion of obviousness, alone, is not sufficient to establish a *prima facie* case. One requirement in order to establish obviousness is that the cited art must provide a suggestion or motivation to modify the art to achieve the present invention, in addition there must be a reasonable expectation of success in so doing. The teaching or suggestion to modify the art, as well as the reasonable expectation of success, must both be found in the prior art and not in the Applicant's disclosure. *In re Vaeck*, 947 F.2d 488 (Fed. Cir. 1991).

Applicant argues that, while the complexing characteristics of the molecules may be retained or perhaps even enhanced through attachment of various chemical substituents to the ring, the resulting increase in size and change in structure of the molecule may render it ineffective as an intercalating agent. In any event, the reference does not disclose the use of phenanthroline as an intercalating agent, or as a complexing agent. The reference only refers to the use of phenanthroline derivatives. The Examiner has shown no suggestion to modify the prior art in such a manner as to use phenanthroline as an intercalating agent, nor has the Examiner shown any expectation of success in attempting to use the phenanthroline derivatives disclosed in the art as an intercalating agent rather than a complexing agent. The cited reference does not appear to contemplate DNA intercalation at all.

The arguments above apply equally to the Examiner's rejection of both claims 22 and 25.

In view of the above, Applicant respectfully argues that the cited reference does not disclose each and every element of the present invention (namely, it lacks disclosure of the use or suitability of phenanthroline derivatives as intercalating agents). Applicant further submits that the Examiner has failed to establish a *prima facie* case of obviousness. As such, Applicant respectfully requests that this rejection be withdrawn.

The Examiner has also rejected claims 22 and 25 under 35 U.S.C. §103(a) as being unpatentable over Mercer-Smith et al. in view of WO 93/21957. Applicant respectfully disagrees with this assessment. It is Applicant's view that the Examiner has failed to establish a *prima facie* case of obviousness with respect to the combination of the two references.

In order to establish a *prima facie* case of obviousness, the Examiner must point to some motivation or suggestion to combine the references to arrive at the present invention. The teaching or suggestion to modify the art must be found in the prior art and not based upon the Applicant's disclosure. *In re Vaeck*, 947 F.2d 488 (Fed. Cir. 1991). The Examiner relies on the statement in the WO 93/21957 reference that "any radioactive metal can be used" to establish that it would have been obvious to use Tc, Re or Mn in the primary reference. But the Examiner is moving backward. The WO 93/21957 statement that any radioactive metal can be used means that any radioactive metal can be used in the WO 93/21957 invention. It certainly does not mean that any radioactive metal can be used in Mercer-Smith et al., and there is nothing in Mercer-Smith to suggest that this is the case. The Examiner is relying on a statement made in WO 93/21957 to draw a conclusion about the Mercer-Smith et al. reference, when in fact there is no

reason to believe that WO 93/21957 were referring to Mercer-Smith et al. in any way. The logic used by the Examiner simply does not follow in this particular instance. Thus, there is no motivation in the prior art to combine the two references, nor is there any support for a reasonable expectation of success in using Tc, Re, or Mn in the conjugate of Mercer-Smith et al.

The argument above applies equally to the Examiner's rejection of both claims 22 and 25.

In view of the above, Applicant submits that the Examiner has failed to establish a *prima facie* case of obviousness (namely, the Examiner has failed to establish a motivation to combine the references or a reasonable expectation of success in such a combination). As such, Applicant respectfully requests that this rejection be withdrawn.

The Examiner also rejects claims 22 and 25 under 35 U.S.C. §1039a) as being unpatentable over WO 93/21957 in view of Applicant's admission on pages 2-4 of the specification. Applicant respectfully disagrees with this assessment.

All of the arguments made above with respect to the rejection of claims 22 and 25 under 35 U.S.C. §103(a) as being unpatentable over WO 93/21957 are applicable here as well, and Applicant hereby incorporates by reference those arguments in their entirety. In short, the complexing agents (phenanthroline derivatives) of WO 93/21957 do not render the present claims obvious for all of the reasons discussed above.

These arguments again apply equally to Examiner's rejection of both claims 22 and 25.


In view of the above, Applicant respectfully argues that the cited reference does not

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disclose each and every element of the present invention (namely, it lacks disclosure of the use or suitability of phenanthroline derivatives as intercalating agents). Applicant further submits that the Examiner has failed to establish a *prima facie* case of obviousness. As such, Applicant respectfully requests that this rejection be withdrawn.

Applicant respectfully requests that a timely Notice of Allowance be issued in this case.

Respectfully submitted,

A handwritten signature in black ink, appearing to read "L. E. Evans", is written over a horizontal line.

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